REMARKS

Claims 12 to 22 and 24 to 32 are pending in the application. Claims 12, 17, 19, 21, and 32 have been amended, and claims 13, 22, 29, and 31 have been cancelled, herein. No new claims have been added. Following entry of the amendments, claims 12, 14 to 21, 24 to 28, 30, and 32 will be pending in the application.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

I. Alleged Indefiniteness

Claims 12 to 22 and 24 to 32 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for recitation of the phrase "capable of." The Office Action asserts that the phrase "capable of" is vague and indefinite because it is unclear whether a molecule that is capable of performing a recited function actually performs the function. (Office Action dated October 22, 2002, page 2). Without conceding the correctness of the assertion, and to advance prosecution by further clarifying the claimed subject matter, claims 12, 19, 21, and 32 have been amended to replace the phrase "a molecule that is capable of interacting with tumor/host communication pathways" with the phrase "endostatin, angiostatin, thrombospondin, or prolactin." Support for the amendment is found in the specification as filed at, for example, page 6, lines 22 to 28. In addition, claim 17 has been amended to delete the phrase "capable of being." Support for the amendment is found in the specification as filed, at, for example, page 7, line 29 to page 8, line 2. Applicants respectfully submit that the rejection has been obviated, and respectfully request withdrawal thereof.

II. Alleged Lack of Written Description

Claims 12 to 22, 24 to 28, 30, and 32 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of written description because a representative number of species of molecules that inhibit the growth of CNS tumors and interact with tumor/host communication pathways are allegedly not disclosed in the specification. (Office Action dated October 22, 2002, pages 3 to 4). Without conceding the correctness of the assertion, and to advance prosecution by further clarifying the claimed subject matter, as discussed above, claims 12, 19, 21, and 32 have been amended to replace the phrase "a molecule that is capable of interacting with tumor/host communication pathways" with the phrase "endostatin, angiostatin, thrombospondin, or prolactin." Support for the amendment is found in the specification as filed at, for example, page 6, lines 22 to 28. Applicants respectfully submit that the rejection has been obviated, and respectfully request withdrawal thereof.

III. Alleged Lack of Enablement

Claims 12 to 22 and 24 to 32 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse the rejection because the Office Action has failed to meet its burden of establishing a reasonable basis to question the enablement provided for the subject matter defined by the present claims.

"The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that ***defined by the claim(s) of the particular application or patent.***" M.P.E.P. § 2164 (emphasis added).

When making an enablement rejection, the Examiner bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed

invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and ***to back up assertions of its own with acceptable evidence or reasoning*** which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971)(emphasis added). Acceptable support for an enablement rejection can take the form of ***specific findings of fact, supported by the evidence***. M.P.E.P. § 2164.04.

Applicants respectfully submit that the specification enables those skilled in the art to make and use the full scope of the subject matter defined by the pending claims without undue experimentation. Claims 12, 14 to 21, 26, and 32 recite compositions comprising encapsulated producer cells that express a molecule that, in turn, is an inhibitor of the growth of a CNS tumor, wherein the molecule is endostatin, angiostatin, thrombospondin, or prolactin. Claims 24 and 25 recite methods of producing the compositions of claim 12. As discussed above, the invention that one skilled in the art must be enabled to make and use is that ***defined by the claims.*** The Office Action acknowledges that the specification is enabling for an encapsulated producer cell that expresses an inhibitor of the growth of a CNS tumor and affects neovascularization in rats. Accordingly, as acknowledged in the Office Action, the specification enables the full scope of the subject matter defined by claims 12, 14 to 21, 24 to 26, and 32, and Applicants request withdrawal of the enablement rejection with respect to those claims.

Applicants respectfully submit that the Office Action has failed to meet its burden of establishing that the subject matter defined by claims 27, 28, and 30 is not enabled by the specification. As previously discussed, the Office Action acknowledges that the specification is enabling for an encapsulated producer cell that expresses an inhibitor of the growth of a

CNS tumor and affects neovascularization in rats, but asserts that the specification does not provide enablement for encapsulated producer cells that express an inhibitor of the growth of CNS tumors and affect neovascularization in any animal. (Office action dated October 22, 2002, page 4). Applicants respectfully submit, however, that the Office Action has failed to provide credible evidence of unpredictability in the art, and has therefore failed to establish a reasonable basis to question the enablement provided for the subject matter defined by claims 27, 28, and 30.

The Office Action issued March 29, 2002 asserts that Visted, *et al.*, *Neuro-Oncology*, July 2001, 201-210 (hereinafter "the Visted reference") demonstrates that the use of encapsulated cell technology for the treatment of CNS tumors is unpredictable. In the Request for Reconsideration filed July 29, 2002, Applicants provided an explanation as to why the Visted reference does not demonstrate unpredictability in the art. Although the assertion of unpredictability in the art as allegedly demonstrated by the Visted reference has been repeated in the present Office Action, there are several reasons why the assertion is believed to be improper.

First, Applicants' disclosure overcomes the problems identified in the Visted reference with respect to host reactions against the implant. The Office Action asserts that the Visted reference demonstrates that the art is unpredictable because the reference states that limited graft survival may occur due to host immune reactions against the implant, which is often associated with fibrotic outgrowth of the capsules. (Office Action dated October 22, 2002, page 9). The Visted reference goes on to state, however, that "[r]ecent reports however, suggest that the purity of the alginate is ***the vital factor*** for successful grafting. Commercial alginates (not ultrapurified) have been shown to contain 20 to 30 mitogenic impurities that can elicit fibroblast activation." (Page 205)(citations omitted)(emphasis

added). The present specification, in fact, indicates that alginates of high purity and particular G content were specifically chosen for use in the claimed compositions and methods due to the fact that such alginates ***are not immunogically activating***. (See page 10, lines 9 to 28 of the specification as filed).

In addition, the Visted reference also indicates that the location of the implant may result in circumvention of the host's immune response. The reference states that "[t]he CNS may actually represent a suitable site for implantation because of its specific immunologic status. The immune responses in the CNS are mainly cellular, and the alginate provides a barrier against cell-mediated (lymphocytes, natural killer cells, or microglia) destruction of the producer cells." (Page 205). In this regard, the present specification indicates that, due to lack of fibroblasts in the CNS, fibrotic overgrowth was not observed when alginate-encapsulated cells were implanted in rat brains. (See page 42, lines 9 to 29 and page 38, line 14 to page 39, line 12 of the specification as filed). Moreover, the specification indicates that the alginate-encapsulated cells did not induce either a T cell or a B cell response. (See, for example, Table 1, page 39, lines 3 to 12 of the specification as filed). Notably, the studies to which the Visted reference refers as indicating that host immune responses occurred against implanted cells ***did not involve implantation of encapsulated cells into the CNS***. Accordingly, the specification indicates that the implantation of Applicants' non-immunogically activating alginate into the CNS overcomes any problems that may have previously existed with respect to host reactions against implanted alginate-encapsulated cells.

Second, although the Office Action asserts that "there is no evidence presented that the limited graft survival would not occur in humans, even though it does not occur in animals," the Office Action has failed to provide any evidence that limited graft survival

would occur when producer cells encapsulated with Applicant's ***non-immunogically activating alginate*** are implanted into the ***CNS*** of any organism, including humans. The Office Action has failed to satisfy its burden of providing evidence that the art is unpredictable with respect to the implantation of non-immunogically activating alginate into the CNS. Accordingly, the Office Action has failed to provide a reasonable basis to question the enablement provided for the subject matter defined by the claims, *i.e.*, implantation of alginate-encapsulated producer cells ***in the CNS***.

Third, although the Office Action asserts that the Visted reference demonstrates unpredictability in the art because the reference states that alginates could ***theoretically*** elicit a brisk glial reaction that could abolish any therapeutic benefits, (page 205, emphasis added), a statement setting forth a theoretical possibility does not constitute ***evidence*** of unpredictability in the art. Theoretical possibilities simply do not rise to the level of actual evidence of unpredictability, nor do they provide a reasonable basis to assume that the art is unpredictable. Accordingly, the statement from the Visted reference does not constitute acceptable ***evidence*** or ***reasoning*** that establishes a reasonable basis to question the enablement provided in the specification.

The Office Action asserts that, without any evidence that a brisk glial reaction would not occur, the issue remains unpredictable because "even theoretical problems indicate unpredictatility." (Office Action dated October 22, 2002, page 10). Applicants, however, are not required to prove that the theoretical possibility of a glial reaction (or any other theoretical possibility) would not occur to satisfy the enablement requirement. The ***Patent Office*** bears the burden of providing ***actual evidence*** that the problem ***would*** occur to establish lack of enablement. Applicants respectfully submit that the Office Action has not

met this burden, and has failed to establish a reasonable basis to question the enablement provided for the subject matter defined by the claims.

Finally, the Office Action contends that the Visted reference demonstrates that the art is unpredictable because the reference asserts that a host's tolerance to xenografts of encapsulated biomaterial appears to vary between species, and if specific microcapsules are well tolerated in small molecules, testing in large animals is necessary prior to clinical application. (Office Action dated October 22, 2002, page 10). The study to which the Visted reference refers as indicating that a host's tolerance to xenografts varies between species ***did not involve implantation of encapsulated cells into the CNS***. Accordingly, the Visted reference does not provide credible evidence that the art is unpredictable ***with respect to the subject matter defined by the claims***.

Applicants respectfully submit that the Office Action has failed to establish a reasonable basis to question the enablement provided for subject matter defined by claims 27, 28, and 30. Applicants, accordingly, respectfully request withdrawal of the enablement rejection with respect to those claims.

IV. Alleged Obviousness

Claims 12 to 16, 18 to 20, 22, 26 to 29, 31, and 32 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over PCT Application No. WO 97/38707 (hereinafter "the Aebischer application") in view of U.S. Patent No. 5,459,054 (hereinafter "the Skjak-Brek patent") and O'Reilly, M.S., *et al.*, *Cell* 88:277-285 (1997) (hereinafter "the O'Reilly reference"). Applicants respectfully traverse the rejection because the Office Action has failed to provide objective evidence that those of ordinary skill in the art would have been

motivated to combine the cited references, and has therefore failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the PTO must satisfy three requirements. First, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). Second, the proposed modification or combination of the prior art must have had a reasonable expectation of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Conclusory statements attesting to the existence of a motivation or suggestion to combine references do not provide sufficient support for an obviousness rejection. ***Objective evidence*** of a teaching, motivation or suggestion to select and combine references ***must be made of record*** by the Patent Office to properly establish *prima facie* obviousness. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002). Referring to the extensive precedent supporting this tenet of patent law, the Federal Circuit recently stated that "[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on ***objective evidence of record***. This precedent has been reinforced in myriad decisions, and cannot be dispensed with...The need for ***specificity*** pervades this authority." *Id.* (citations omitted)(emphasis added). In addition, the Federal Circuit also recently reiterated the

prohibition against the use of a patent specification as a template for piecing together teachings from multiple references in support of an obviousness rejection, stating that "[i]t is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to 'use that which the inventor taught against its teacher.'" *Id.* at 1434 (citing *W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)).

The Office Action has failed to identify, and has thus failed to make of record, credible evidence of a motivation, teaching, or suggestion that would have led persons of ordinary skill in the art to combine the teachings of the Aebischer application with those of the Skjak-Brek patent and the O'Reilly reference. In fact, none of the references contain a disclosure, teaching, or suggestion that would have led to their combination. The Aebischer application describes implantation of encapsulated cells that express an apoptosis-inducing molecule into the CNS. The application, however, fails to teach, disclose, or suggest encapsulation of cells that produce endostatin. The Skjak-Brek patent describes alginate-encapsulated cells, but does not teach, disclose, or suggest encapsulated cells that express a non-endogenous protein, much less encapsulated cells that express endostatin. The O'Reilly reference describes the isolation of endostatin, and the expression of recombinant endostatin in *E. coli* and Baculovirus cells. The O'Reilly reference fails to teach, disclose, or suggest that endostatin is an inhibitor of CNS tumors, and fails to teach or suggest alginate encapsulation of cells expressing endostatin for the treatment of CNS tumors. Accordingly, the Aebischer application, the Skjak-Brek patent, and the O'Reilly reference each do not contain a disclosure or suggestion that would have led those of ordinary skill in the art to combine their teachings.

Although the Office Action asserts that those of ordinary skill in the art would have been motivated to combine the teachings of the cited references because the Aebischer

application teaches that "cells expressing therapeutic molecules can be used treat [*sic*] CNS tumors when they are encapsulated in a matrix that protects the cell from the host's immune response," (Office Action dated October 22, 2002, page 12) the Office Action has failed to provide any evidence that those of ordinary skill in the art would have been motivated to encapsulate cells that express ***endostatin*** for the treatment of CNS tumors. Accordingly, Applicants respectfully submit that the Office Action has failed to make of record any objective evidence that those of ordinary skill in the art would have been motivated to combine the teachings of the cited references, and has therefore based the assertion of obviousness on impermissible hindsight reconstruction.

Moreover, assuming *arguendo* that those of ordinary skill in the art would have been motivated to combine the teachings of the cited references, which Applicants do not concede, the combination would not have produced a claimed invention. For example, none of the cited references disclose or suggest compositions comprising encapsulated producer cells that express ***angiostatin, thrombospondin, or prolactin***. Accordingly, Applicants respectfully request withdrawal of the rejection.

Information Disclosure Statement

Applicants submitted an Information Disclosure Statement and accompanying 1449 Form to the Patent Office on May 11, 2001. Applicants have not yet received a signed and initialed copy of the 1449 Form. Enclosed is an additional copy of the 1449 Form and a copy of the return post card indicating that the Information Disclosure Statement, 1449 Form, and 24 listed documents were received by the Patent Office on May 11, 2001. Applicants respectfully ask the Examiner to initial and sign the 1449 Form and return the form to Applicants, confirming consideration of the listed documents.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claims 12, 17, 19, 21, and 32 have been amended as follows.

12. (Twice Amended) A composition comprising a producer cell that expresses a molecule that is an inhibitor of the growth of a CNS tumor, the cell being encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, wherein the molecule is [: a molecule that is capable of interacting with tumor/host communication pathways] endostatin, angiostatin, thrombospondin, or prolactin.

17. (Amended) The composition according to claim 12, wherein the cell's expression of [the molecule] endostatin, angiostatin, thrombospondin, or prolactin is [capable of being] switched on and off by an external pharmacological agent.

19. (Twice Amended) A composition comprising a producer cell that expresses a molecule that is an inhibitor of the growth of a CNS tumor, the cell being encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%, wherein the molecule is [a molecule that is capable of interacting with tumor/host communication pathways,] endostatin, angiostatin, thrombospondin, or prolactin and [wherein] the CNS tumor is a brain tumor.

21. (Twice Amended) A composition comprising a producer cell that expresses a molecule that is an inhibitor of the growth of a CNS tumor, the cell being encapsulated in a matrix that comprises an immunoisolating alginate having a G content of above 15%,

wherein the molecule is [a molecule that is capable of interacting with tumor/host communication pathways,] endostatin, angiostatin, thrombospondin, or prolactin and [wherein] the producer cell is encapsulated in a bead or microbead and the alginate concentration within the bead or microbead increases from the center of the bead or the microbead to the outer rim.

32. (Amended) The composition according to claim 12 wherein the producer cell comprises a plasmid that includes a nucleic acid sequence that encodes [a protein that is capable of interacting with tumor/host communication pathways] endostatin, angiostatin, thrombospondin, or prolactin.

Claims 13, 22, 23, 29, and 31 have been cancelled.